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Renal Responses to Graded Hemorrage in Conscious Pigs

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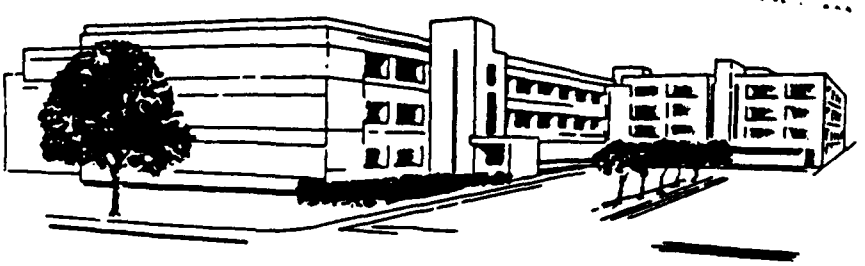

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We developed a conscious pig model with a chronically instrumented kidney to measure renal blood flow, glomerular filtration rate, and excretory functions during hemorrhage. Seven to ten days prior to experimentation, pigs were splenectomized, arterial and venous catheters implanted, an ultrasonic flow probe placed on the renal artery, and a pyelostomy performed for non-occlusively placing a ureteral catheter. Measurements were taken prior to hemorrhage, and at hemorrhage volumes of 7, 14, 21, and 28 ml/kg, or at corresponding time points for controls. Renal blood flow, glomerular filtration rate, urine flow rate, osmotic and electrolyte excretion, and arterial pressure decreased progressively to hemorrhage volumes of 14 ml/kg or greater. Thus, pigs, like humans, respond to hypovolemia with redistribution of blood flow away from the kidney. This differs from the dog, which shows no

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change in renal blood flow or glomerular filtration rate until severe hypotension. Therefore, as an animal model for studying renal hemodynamics during hemorrhage, the conscious pig, in its similarity to the human, is superior to the dog.

ABSTRACT

We developed a conscious pig model with a chronically instrumented kidney to measure renal blood flow, glomerular filtration rate, and excretory functions during hemorrhage. Seven to ten days prior to experimentation, pigs were splenectomized, arterial and venous catheters implanted, an ultrasonic flow probe placed on the renal artery, and a pyelostomy performed for non-occlusively placing a ureteral catheter. Measurements were taken prior to hemorrhage, and at hemorrhage volumes of 7, 14, 21, and 28 ml/kg, or at corresponding time points for controls. Renal blood flow, glomerular filtration rate, urine flow rate, osmotic and electrolyte excretion, and arterial pressure decreased progressively to hemorrhage volumes of 14 ml/kg or greater. Thus, pigs, like humans, respond to hypovolemia with redistribution of blood flow away from the kidney. This differs from the dog, which shows no change in renal blood flow or glomerular filtration rate until severe hypotension. Therefore, as an animal model for studying renal hemodynamics during hemorrhage, the conscious pig, in its similarity to the human, is superior to the dog.

INTRODUCTION

The compensation to hemorrhage includes redistribution of blood flow from peripheral organs to the critical organs, brain and heart (1). If vasoconstriction to peripheral organs has been prolonged and severe enough, organ failure may ensue even though blood pressure and blood volume are adequately restored (2). During the Korean conflict, before rapid transport of injured patients became standard practice, posttraumatic renal failure occurred at a rate of 35% (3). Even today, acute renal failure following major trauma is associated with a mortality of 90% (3). Therefore, development of an animal model for study of renal function during hemorrhage is highly pertinent.

The cardiovascular and renal systems of swine are more similar to the human than are the systems in other species such as the dog, rat or sheep (1). In fact, the pig is the only species except for the dwarf-water buffalo which has a multipyramidal kidney similar to humans (1). In addition, the pig is similar to man in that it has predominantly short-looped nephrons (pig: 97% vs man: 86%) in contrast to the dog which has 100% long-looped nephrons (4). For these reasons, we measured renal function in the conscious pig during hemorrhage. It is very important to use conscious animals since it has been shown that anesthesia alters responses to hemorrhage (5-7). We show that responses of pigs to hemorrhage are similar to those of man (8) since renal blood flow and glomerular filtration rate are both decreased as well as electrolyte excretion. We discuss how this contrasts with the dog, since the dog does not alter its renal blood flow until the degree of hemorrhage is severe (5,6).

METHODS

Surgical preparation. Twenty-one immature female Yorkshire/Duroc swine (J.G. Boswell, Corcoran, CA) weighing 20-25 kg were used in this study. The animals were fasted 24 hours before surgery with water available ad lib. On the morning of surgery, the pigs were premedicated with ketamine HCl (2.2 mg/kg), xylazine HCl (2.2 mg/kg), and atropine (0.1 mg/kg), anesthetized with halothane using a snout mask, and maintained after intubation on a mixture of halothane

(1%), N_2O and O_2 on a ventilator. All surgery was performed using aseptic techniques.

The spleen was removed (via a midline laparotomy) because the pig has a contractile spleen which may increase the variability in the response to hemorrhage. A catheter was inserted into the splenic vein and its tip advanced into the portal vein. The left kidney was approached through the midline incision. The ureter was non-occlusively catheterized through a pyelostomy made on the ventral surface of the ureter near its junction with the renal pelvis. A 10-French pediatric Malecot catheter was passed through the pyelostomy toward the kidney and secured with a purse-string suture. Patency of the ureter lumen was determined by injecting saline through the catheter and observing passage of the saline down through the ureter. To test whether the purse-string suture was adequately secured, gentle pressure was applied after filling the ureter proximal and distal to the catheter with saline and noting that no leakage occurred from the incision site. A snare of PE-160 tubing was placed around the ureter approximately 2 cm distal to the Malecot catheter. The ends of the tubing were threaded through a PE-350 sleeve. An ultrasonic flow probe (6 mm, Transonic Systems, Inc., Ithaca, NY) was placed around the renal artery for measuring renal blood flow. The leads and distal ends of the catheters were coiled in the retroperitoneal space adjacent to the kidney. The peritoneum was closed and the laparotomy incision was sutured in layers.

The pig was repositioned onto its right side and a left flank incision was made. A large bore polyvinyl catheter (0.125 inch i.d.) was implanted non-occlusively in the infrarenal aorta. This catheter was used for blood withdrawal and monitoring blood pressure. The Malecot, vascular catheters, and flow probe cable were exteriorized through the lumbar muscle to the back and protected with a Velcro patch. Through a midline incision in the neck, a 5 French pediatric Swan-Ganz catheter was inserted through the left external jugular vein so that its tip was in the pulmonary artery. This catheter was used for cardiac output determinations using the thermodilution method. The catheters were flushed and subsequently filled with a heparin solution (100 U/ml) daily to maintain patency. Keflin (1 g/day) was administered on the day of and for three days following surgery to prevent infection. The entire post-operative recovery was

monitored and appropriate treatment administered if needed.

Experimental Protocol. The pig was fasted 18 h prior to the experiment with water available ad lib. For the experiment, the pig was placed in a modified Pavlov sling. An extension tube was connected to the ureteral catheter, the snare was tightened to occlude flow distally and urine was allowed to flow freely into a graduated cylinder. The arterial and Swan-Ganz catheters and the flow probe were connected to a pressure transducer (Statham Gould, Oxnard, CA) and polygraph (Gould, Cleveland, OH), a cardiac output computer (Gould, Cleveland, OH), and an ultrasonic blood flow meter (Transonic, Ithaca, NY), respectively.

A period of 60 min was allowed for the animal to become accustomed to the surroundings before a pre-hemorrhage clearance measurement was taken. A clearance measurement consisted of a 20 min urine collection with an arterial sample (12 ml) taken at the midpoint. Following the control period, 28 ml/kg blood was removed continuously over 44 min in a logarithmic fashion to mimic a hemorrhage from a severed artery. To achieve this, blood was removed in 7 ml/kg increments, i.e., 7 ml/kg over 9 min, then over 10 min, then 12 min, and 13 min. A 12-ml aliquot of the shed blood was collected at the end of each bleed period or a 12-ml sample was collected at the same time period in the time control experiments. The blood samples were heparinized and the plasma removed following centrifugation. The urine flow rate, renal blood flow, and blood pressure were measured at the end of each period. In addition, cardiac output was measured at the end of the hemorrhage.

After the experiment, the animal was euthanized with an intravenous overdose of barbiturate. A gross necropsy examination was performed. The external length and width of the kidney, and the diameter of the origin of the ureter were measured. The kidney was sectioned sagittally and internal measurements were taken of the length and width of the medulla and the thickness of the cortex. A tissue sample was taken for histological evaluation. To ascertain whether the observed changes were due to the preparation or due to inherent size differences between right and left kidneys, kidneys from animals used in other studies not involving surgical manipulation were harvested and measured.

Sample analyses. Concentrations of sodium, potassium and creatinine in the plasma and urine samples were measured using an autoanalyzer (Roche Diagnostic Systems, COBAS FARA Model, Nutley, NJ) with ion specific electrodes for the sodium and potassium and a modifed Jaffe method (2) for the creatinine. Plasma and urine osmolalities were measured with a freezing-point depression osmometer (Advanced III, Needham Hts, MA). Hematocrit was measured in duplicate by the microcapillary method (IEC MB Centrifuge, Needham Hts, MA).

Calculations. Clearances were calculated for creatinine, sodium, potassium, and osmolality. The formula is as follows: $Clearance_x = (U_x \times V)/P_x$, where U_x is the urine concentration of substance x, V is the urine flow rate (ml/min), and P_x is the plasma concentration of x. Free water clearance was calculated by subtracting the osmotic clearance from the urine flow rate. Creatinine clearance was used to estimate glomerular filtration rate (GFR). The fractional excretion was calculated by dividing the clearance of sodium or potassium by GFR. Renal plasma flow (RPF) was estimated by dividing the RBF measured with the flow probe by the calculated plasma fraction. Filtration fraction was calculated by dividing the GFR by the RPF.

Statistical analysis. The following analyses were performed on the hemodynamic and renal function data. An unpaired t-test was performed to determine whether the baseline values were similar between the groups (10). To ascertain whether changes occurred with time and within a group, a one-way analysis of variance with repeated measures was performed (11). To ascertain whether there was a difference between the time control and hemorrhage groups, a two-way analysis of covariance was performed with repeated measures on the time factor and non-repeated measures between the treatment groups (11). The value at time 0 was used as the covariate. If there was a significant difference, a Newman-Keuls multiple range test was performed to determine which values were significantly different (10). A P value less than 0.05 was considered significant. The data are expressed as means ± SEM.

For the anatomical dimension data, a two-way analysis of variance was performed with repeated measures for the comparison between the instrumented and contralateral control kidney, and non-repeated

measures for the comparison between right and left kidneys of the experimental pig versus the intact pig (11). There was no statistical analysis performed for the histological evaluation data.

RESULTS

Hemodynamic and renal responses. The mean arterial pressure (MAP), single kidney blood flow (RBF), and single kidney urine flow (V) responses during the time control and hemorrhage are shown in Figure 1. At 19 min, RBF was reduced from the pre-hemorrhage control value by 30%, a time with no significant change in MAP or V. This reduction of RBF occurred at the hemorrhage volume of 14 ml/kg. Using a value of total blood volume of 67 ml/kg for immature swine measured in a previous study (12), this hemorrhage volume is estimated to be 21% of the total blood volume. When an estimated 31% of the blood volume was removed at 31 min, V was significantly reduced by 74%, RBF was reduced by 48%, and MAP was reduced by 32%, although this change in MAP did not reach statistical significance. At 44 min, with a hemorrhage volume estimated to be 42% of the total blood volume, MAP was decreased by 53%, RBF by 74%, and V by 90%. Table I shows the response of cardiac output (CO) and derived variables, total peripheral resistance (TPR) and total RBF expressed as a percentage of CO. CO was reduced by 43% after the 28 ml/kg hemorrhage. There was no significant change in the calculated TPR at that volume of hemorrhage. The %RBF/CO was decreased by 54%.

Table II shows the single kidney renal hemodynamic and urinary excretory responses to the graded hemorrhage. Renal vascular resistance almost doubled (+84%) at the 28 ml/kg volume of hemorrhage. Glomerular filtration rate (GFR) paralleled RBF such that GFR was reduced by 44%, 64%, and 80% at the 14, 21, and 28 ml/kg hemorrhage volumes, respectively. Filtration fraction did not significantly change in response to hemorrhage.

The hematocrits were decreased by 10, 16, and 24% at the 14, 21, and 28 ml/kg hemorrhage, respectively (Table II). Reflecting the decreased GFR, plasma creatinine concentrations were significantly increased by 10% and 24% at the 21 and 28 ml/kg hemorrhages, respectively.

Osmotic clearance, sodium and potassium excretion, and the fractional excretion of sodium and potassium decreased in response to hemorrhage (Table III). There was no significant change in the free-water clearance. Table III includes values of zero when there was no urine flow. However, the trend is similar to the results of the 5 of 11 animals who did maintain some urine flow during the hemorrhage.

Kidney measurements. Various anatomical measurements of the kidney were made to determine whether instrumentation had caused any gross changes in kidney structure. We compared the instrumented left kidney with the intact contralateral kidney. We also made similar measurements of the left and right kidneys of pigs whose kidneys were not instrumented. These measurements are depicted in Table IV and correspond to measurements at locations shown in Figure 2. The only significant differences found were a 17.5% increase in external kidney width and 54.8% increase in ureter diameter. The size of the kidney parenchyma was not altered by this preparation.

Histological evaluation. We also performed a histological examination of the instrumented and the contralateral control kidney for evidence of microscopic abnormalities. The results are shown in Table V. All categories of lesions were more frequently seen in the instrumented kidneys than in the contralateral kidneys, and therefore the lesions were attributed to the surgical intervention rather than the experiment itself. Minimal to marked inflammation of the renal capsule was found in the majority of the instrumented kidneys, but only rarely in the contralateral control kidney. There were also some incidences of minimal to marked cases of pyelonephritis in both kidneys although the incidence was higher and the severity greater in the instrumented kidneys. The pyelonephritis was consistent with an inflammatory response probably resulting from surgical manipulation or catheter-associated localized trauma. There was no dilation of cortical or medullary tubules which would have been observed had ureteral stasis occurred. No indication of bacterial infection in the kidneys was visible. Cortical necrosis and arterial endothelial proliferation were found in several cases and only involved the instrumented kidney. The cortical necrosis was due to infarction in 2 of the 3 cases. They are thought to be due to manipulation of the kidney or due to the presence of the flow probe. These

observations apply only to the sections examined, which were a small portion of the total kidney.

DISCUSSION

Our results indicate that the conscious pig responds to hemorrhage by redistributing blood flow away from the kidney, even at hemorrhage volumes which do not significantly reduce MAP (Figure 1). Humans also show a similar response. Stone and Stahl (8) measured a 25% decrease in RBF and GFR in normal, supine humans in response to a 15-22% hemorrhage which caused a 18 mmHg (22%) decrease in MAP. In another model of mild hypovolemia, head-up tilt, humans also responded with a decrease in RBF and GFR, but without any decrease in MAP (13). This is in sharp contrast to the response shown by conscious dogs. With a hemorrhage volume as large as 26 ml/kg, which decreased MAP by 20-30 mmHg, the dog maintains its RBF and GFR (5,6). Likewise, anesthetized pigs do not respond to hemorrhage with decreases in RBF and GFR until severe hypotension occurs (14,15). Since renal failure is a serious complication of shock (3), it is critical to select a model which mimics the responses found in man.

Whether or not there is a decrease in RBF or GFR, hemorrhage induces an antidiuresis in all species (Figure 1)(8,14,16). In fact, it has been observed that oliguria is one of the earliest signs of acute hemorrhage in normal man (8). Urine output is often used as an endpoint of fluid resuscitation in trauma patients. Osmotic and electrolyte excretion also decreased in response to hypotensive hemorrhage (Table III)(8,16). In anesthetized pigs, Shackford (17) did not observe a decrease in sodium excretion although GFR fell. In the present study, when corrected for changes in GFR, sodium and potassium clearances did not decrease until the 28 ml/kg volume, indicating that electrolyte excretion paralleled GFR until severe hypotension was present (Table III). There was also a tendency, although not statistically significant, for the free-water clearance to decrease in the present study (Table III). In man, free-water clearance did not change in response to a moderate hemorrhage (8).

In the present study, TPR did not change during hemorrhage (Table I), indicating a parallel decrease in CO and MAP. This lack of a change in TPR has also been seen in anesthetized pigs (calculated from data in 17).

The renal vascular resistance (RVR) tended to increase at hemorrhage levels greater than 7 ml/kg and reached significance at 28 ml/kg hemorrhage (Table II). Stone and Stahl (8) found that RVR increased following hemorrhage in man, although the magnitude of that response was small. However, the smaller response seen in their study may be due to the fact that their subjects had been hydrated prior to the study with a 10 ml/kg intravenous infusion of 0.45% NaCl. The conscious dog responds with an increased TPR but with renal vasodilation in response to a moderate hemorrhage (6). With severe hypotension, RVR does increase in the dog (6).

We examined the kidneys histologically to determine whether the instrumentation altered the renal structure in any way that would impinge on kidney function. The ureter and peri-ureteral tissue of the instrumented kidney were still somewhat dilated and edematous at the time of the experiment which was one week following the implantation of the Malecot catheter (Table IV). This catheter-associated, localized trauma was probably the cause of most of the mild cases of pyelonephritis found (Table V), there was no indication of dilated renal tubules indicative of increased ureteral pressure. The capsular inflammation evident in some instrumented kidneys was probably secondary to the surgical manipulation (Table V). However, these histological findings were minor and not considered to be able to affect renal function. The renal hemodynamic and excretory functions were comparable to normal values for swine (14,15,17,18).

This animal preparation has two disadvantages: the immature pig grows rapidly, making comparisons between serial experiments difficult; and, ureteral patency often does not return once the ureteral snare has been tightened to divert urine flow from the bladder to the catheter. When the snare was released in a pilot protocol, and the pig euthanized 24 hours later, hydronephrosis was evident due to the loss of patency and/or ureteral peristalsis (unpublished observations).

In conclusion, the renal responses to hemorrhage in the conscious pig and man display similar patterns of changes in RBF, GFR, and osmolal and electrolyte excretion. These results indicate that it is desirable to use a swine model to study whether hemorrhage leads to an alteration of renal function. Since the

consequences of acute renal failure following major trauma is associated with mortality as high as 90% (12), the conscious swine model offers a powerful tool for the evaluation of pathophysiological mechanisms and therapeutic regimes.

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REFERENCES

1. Terris JM. Swine as a model in renal physiology and nephrology: an overview. In: ME Tumbleson, ed. Swine in Biomedical Research, vol 3. New York: Plenum Press, 1986;1673-1689.

2. Passmore JC. Role of the kidney in shock: current views. In: B.M. Altura et al., eds. Handbook of Shock and Trauma, Vol. 1: Basic Science. New York: Raven Press, 1983;113-128.

3. Sirinek KR, Hura CE. Renal failure. In: K.L. Mattox et al., ed. Trauma. Norwalk, CT: Appleton & Lange, 1988;835-848.

4. Nielsen TW, Maaske CA, Booth NH. Some comparative aspects of porcine renal function. In: L.K. Bustad and R. O. McClellan, eds. Swine in Biomedical Research. Seattle: Frayn Printing Co., 1965;529-536.

5. Kremser PC, Gewertz BL. Effect of pentobarbital and hemorrhage on renal autoregulation. Am J Physiol 1985;249:F356-F360.

6. Vatner SF. Effects of hemorrhage on regional blood flow distribution in dogs and primates. J Clin Invest 1974;54:225-235.

7. Zimpfer M, Manders WT, Barger AC, Vatner SF. Pentobarbital alters compensatory neural and humoral mechanisms in response to hemorrhage. Am J Physiol 1982;243:H713-H721.

8. Stone AM, Stahl WM. Renal effects of hemorrhage in normal man. Ann Surg 1970;172:825-836.

9. Cook JGH. Creatinine assay in the presence of protein. Clin Chem Acta 1971;32:485-486.

10. Zar JH. Biostatistical Analysis. New Jersey: Prentice-Hall, Inc. 1974.

11. Winer BJ. Statistical Principles in Experimental Design Second Edition. New York: McGraw-Hill Book Co. 1971.

12. Hannon JP, Bossone CA, Rodkey WG. Splenic red cell sequestration and blood volume measurement in conscious pigs. Am J Physiol 1985;248:R293-R301.

13. Lee TD, Jr., Lindeman RD, Yiengst MJ, Shock NW. Influence of age on the cardiovascular and renal responses to tilting. J Appl Physiol 1966;21(I):55-61.

14. Maier M, Starlinger M, Zhegu Z, Rana H, Binder BR. Effect of the protease inhibitor aprotinin on renal hemodynamics in the pig. Hypertension 1985;7:32-38.

15. Suarez CA, Guerrero AA, Musil G, Hulet WH. Renal function and nephron structure in the miniature pig. Am J Vet Res 1968;29:995-1007.

16. Edwards BS, Zimmerman RS, Schwab TR, Heublein DM, Burnett JC, Jr. Role of atrial peptide system in renal and endocrine adaptation to hypotensive hemorrhage. Am J Physiol 1988;254:R56-R60.

17. Shackford SR, Norton CH, Ziegler MG, Wilner KD. The effect of hemorrhage and resuscitation on serum levels of immunoreactive atrial natriuretic factor. Ann Surg 1988;207:195-200.

18. Buckley NM, Charney AN, Brazeau P, Cabili S, Frasier ID. Changes in cardiovascular and renal function during catecholamine infusions in developing swine. Am J Physiol 1981;240:F276-F281.

TABLE I. Hemodynamic and renal responses to hemorrhage.

CONDITION	N	BASELINE	44 MIN
			28 ml/kg
		Cardiac Output (L/min)	
Control	10	4.86 ± 0.43	4.65 ± 0.36
Hemorrhage	11	4.42 ± 0.25	2.51 ± 0.23+*
		Total Peripheral Resistance (mmHg/(L/min))	
Control	9	25 ± 2	26 ± 3
Hemorrhage	11	26 ± 2	23 ± 3
		Total Renal Blood Flow/Cardiac Output (%)	
Control	10	12 ± 2	13 ± 2
Hemorrhage	10	11 ± 1	5 ± 1+*

* $P < 0.05$ different from pre-hemorrhage control value

+ $P < 0.05$ different from same time point in time control experiment

TABLE II. Heart rate, hematocrit, and plasma creatinine, renal vascular resistance, glomerular filtration, and filtration fraction responses to hemorrhage.

CONDITION	N	BASELINE	9 MIN 7 ml/kg	19 MIN 14 ml/kg	31 MIN 21 ml/kg	44 MIN 28 ml/kg
Heart Rate (beats/min)						
Control	10	138 ± 8	132 ± 7	129 ± 6	135 ± 9	137 ± 6
Hemorrhage	11	127 ± 4	151 ± 10	165 ± 11+	158 ± 14+	171 ± 19+*
Hematocrit (% RBC)						
Control	10	29.7 ± 1.4	28.9 ± 1.3	28.3 ± 1.4	29.1 ± 1.5	28.9 ± 1.5
Hemorrhage	10	30.5 ± 0.9	29.7 ± 1.2	27.6 ± 1.2+*	25.7 ± 1.2+*	23.1 ± 1.1+*
Plasma Creatinine (mg/dl)						
Control	10	1.01 ± 0.06	1.00 ± 0.06	0.97 ± 0.06	0.97 ± 0.04	1.02 ± 0.05
Hemorrhage	10	0.94 ± 0.03	0.91 ± 0.04	0.96 ± 0.04	1.03 ± 0.04+*	1.17 ± 0.06+*
Renal Vascular Resistance (mmHg/ml/min/kidney)						
Control	9	0.50 ± 0.06	0.51 ± 0.06	0.48 ± 0.06	0.48 ± 0.06	0.49 ± 0.07
Hemorrhage	10	0.50 ± 0.05	0.53 ± 0.09	0.68 ± 0.17	0.75 ± 0.11	0.92 ± 0.09+*
Glomerular Filtration Rate (ml/min/kidney)						
Control	10	27 ± 3	28 ± 4	28 ± 2	28 ± 3	28 ± 3
Hemorrhage	10	25 ± 3	28 ± 5	14 ± 3+	9 ± 3+*	5 ± 3+*
Filtration Fraction (%)						
Control	9	17 ± 2	18 ± 3	17 ± 2	16 ± 2	17 ± 3
Hemorrhage	9	15 ± 2	19 ± 4	12 ± 2	11 ± 3	8 ± 4

+ $P < 0.05$ different from same time point in time control experiment
* $P < 0.05$ different from pre-hemorrhage control value

TABLE III. Osmolal, free-water, and electrolyte excretory responses to hemorrhage.

CONDITION	N	BASELINE	9 MIN 7 ml/kg	19 MIN 14 ml/kg	31 MIN 21 ml/kg	44 MIN 28 ml/kg
			Osmolal Clearance (ml/min/kidney)			
Control	10	0.43 ± 0.07	0.49 ± 0.09	0.49 ± 0.09	0.49 ± 0.10	0.62 ± 0.16
Hemorrhage	10	0.60 ± 0.18	0.59 ± 0.18	0.37 ± 0.14	0.13 ± 0.05+*	0.05 ± 0.05+*
			Free Water Clearance (ml/min/kidney)			
Control	10	0.23 ± 0.09	0.26 ± 0.16	0.24 ± 0.15	0.20 ± 0.14	0.29 ± 0.17
Hemorrhage	10	0.17 ± 0.12	0.10 ± 0.09	0.10 ± 0.05	0.06 ± 0.02	0.02 ± 0.01
			Sodium Excretion (μEq/min/kidney)			
Control	10	27 ± 7	30 ± 8	32 ± 8	34 ± 8	40 ± 15
Hemorrhage	11	49 ± 24	47 ± 23	32 ± 17	12 ± 4	4 ± 3+
			Potassium Excretion (μEq/min/kidney)			
Control	10	16 ± 4	18 ± 4	19 ± 4	16 ± 3	20 ± 5
Hemorrhage	11	13 ± 4	15 ± 4	10 ± 3	4 ± 1+*	1 ± 1+*
			Fractional Excretion of Sodium (%/kidney)			
Control	10	0.77 ± 0.22	0.82 ± 0.22	0.83 ± 0.22	0.95 ± 0.25	0.98 ± 0.29
Hemorrhage	10	0.72 ± 0.21	0.71 ± 0.15	0.74 ± 0.12	0.69 ± 0.14	0.20 ± 0.09+*
			Fractional Excretion of Potassium (%/kidney)			
Control	10	13 ± 3	14 ± 3	14 ± 3	14 ± 3	14 ± 2
Hemorrhage	10	9 ± 2	9 ± 2	11 ± 3	10 ± 3	5 ± 3+

+ $P < 0.05$ different from same time point in time control experiment
* $P < 0.05$ different from pre-hemorrhage control value

TABLE IV. Kidney measurements with letters of parameters corresponding to Figure 2.

		Experimental Pig (n=9)		Intact Pig (n=9)	
		Instrumented Kidney (L)	Contralateral Kidney (R)	Left Kidney	Right Kidney
			External Size (cm)		
A.	Width	4.7 ± 0.2*+	4.1 ± 0.1	4.0 ± 0.2	3.9 ± 0.3
B.	Length	10.0 ± 0.3	9.3 ± 0.2	9.4 ± 0.3	9.4 ± 0.2
C.	Ureter	1.6 ± 0.1*+	1.0 ± 0.09	1.0 ± 0.06	1.1 ± 0.05
			Sagittal Section (cm)		
			Cortex		
D_1.	Anterior	1.0 ± 0.09	0.7 ± 0.06+	0.8 ± 0.05	0.9 ± 0.09
D_2.	Posterior	1.0 ± 0.08	0.8 ± 0.06	0.9 ± 0.06	1.0 ± 0.04
D_3.	Lateral	1.2 ± 0.1	1.2 ± 0.3	1.1 ± 0.07	1.1 ± 0.08
D_4.	Indentation	2.5 ± 0.5	2.3 ± 0.3	1.8 ± 0.07	1.9 ± 0.0
			Medulla		
E.	Length	6.3 ± 0.5	5.2 ± 0.3	6.5 ± 0.8	6.1 ± 0.6
F.	Width	2.6 ± 0.2	2.1 ± 0.1	2.0 ± 0.2	2.2 ± 0.1
			Body Weight (kg)		
		19.3 ± 0.7+		23.6 ± 1.4	

* P<0.05 Difference between instrumented left kidney (L) and contralateral right kidney (R)

+ P<0.05 Difference between experimental pig and intact pig.

TABLE V. Histological evaluation of the lesions found in kidneys from the instrumented kidney and the contralateral non-instrumented kidney from pigs which received time control experiments (CONTROL) and from pigs which received a 28 ml/kg hemorrhage (HEMORRHAGE).

	GRADE OF LESION							
	Instrumented Kidney				Contralateral Kidney			
PIG ID	CN	P-N	CAP IN	AEP	CN	P-N	CAP IN	AEP
CONTROL								
1. 65		2	1					
2. 73		2	1	1				
3. 86	4		3			1		
4. 107		2						
5. 128		3	3			1		
6. 155		1						
7. 165		1						
8. 168		1	4					
9. 179			3	2				
10. 279	4	2	4	3				
# where lesion present	2	8	7	3		2		
HEMORRHAGE								
1. 70		4		1			2	
2. 72		1	2					
3. 74								
4. 82		1	3					
5. 94		3	1			2		
6. 163			2					
7. 206			3	2		1		
8. 219			2					
9. 278		1	3			1		
10. 311			2					
11. 312	1		2					
# where lesion present	1	5	9	2		3	1	

DEFINITIONS:
CN = Cortical necrosis
P-N = Pyelonephritis
CAP IN = Capsular Inflammation
AEP = Arterial Endothelial Proliferation

GRADING SCHEME:
1 = Minimal
2 = Mild
3 = Moderate
4 = Severe

FIGURE LEGENDS

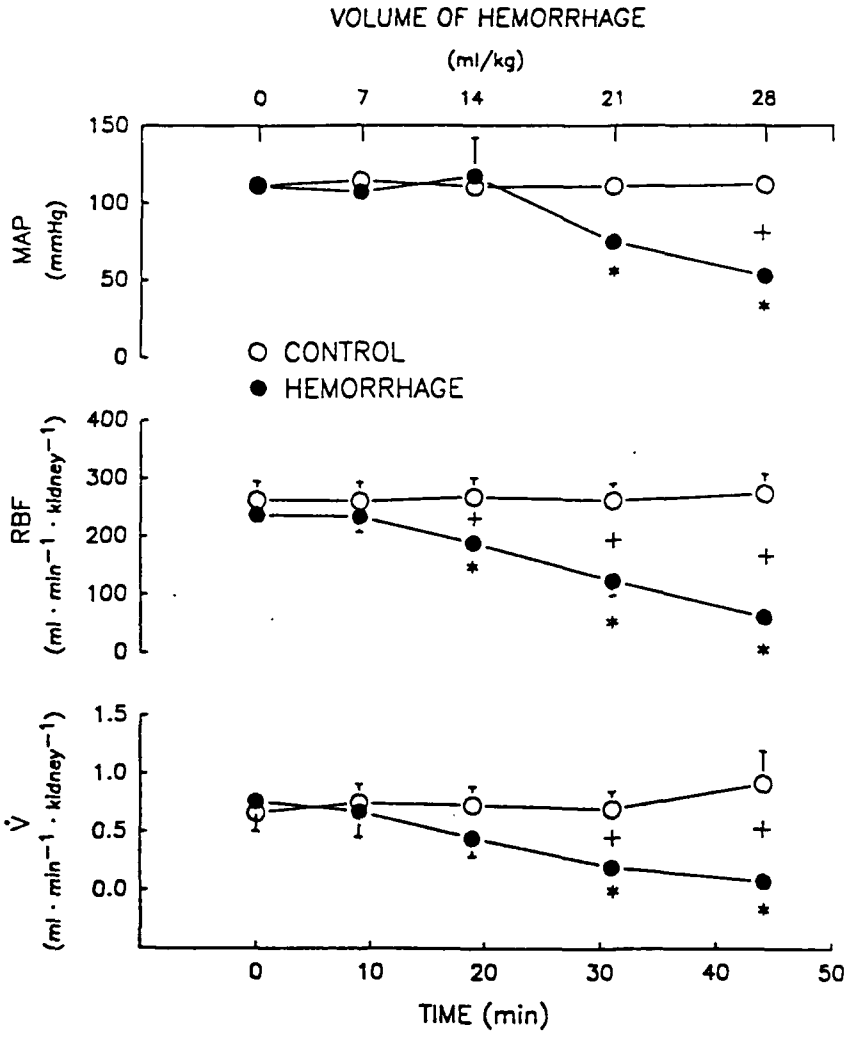

Figure 1: Mean arterial pressure (MAP), renal blood flow (RBF), and urine flow rate (V) responses during hemorrhage (n=10) or a time control experiment (n=11). * $p < 0.05$ different from the pre-hemorrhage control value (time 0). + $p < 0.05$ different from same time point during the time control experiment. Data are expressed as means ± SE.

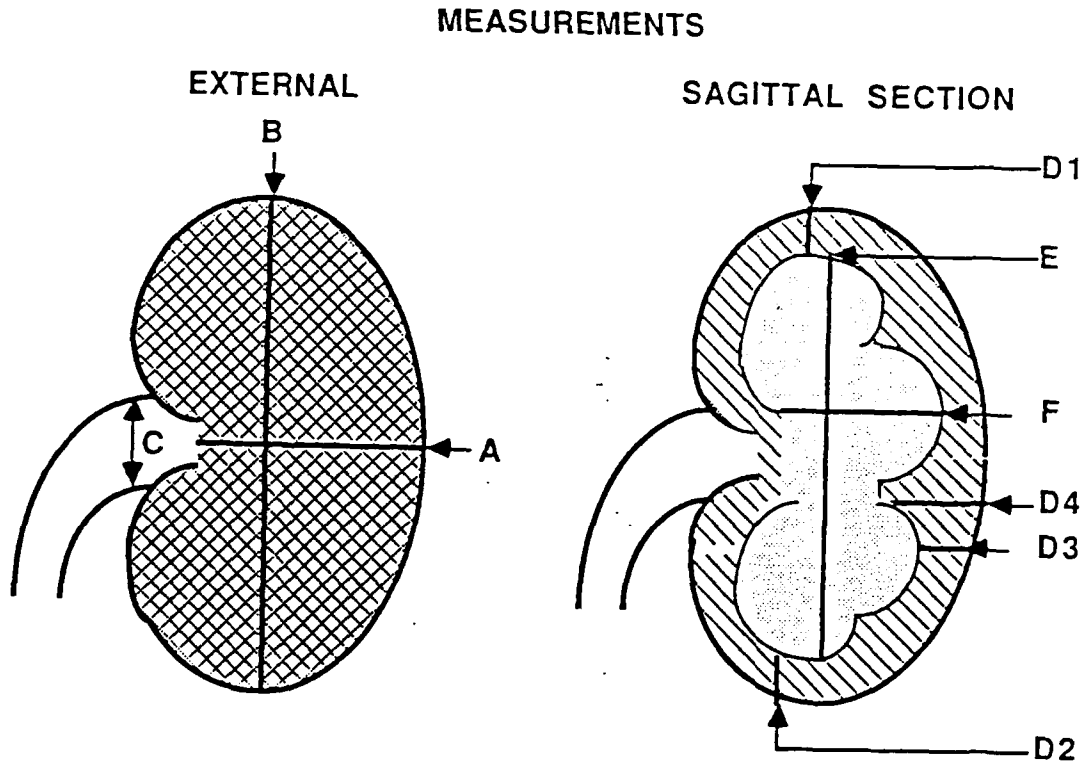

Figure 2: The letters depict where measurements were made to assess whether the instrumentation of the kidney caused any gross anatomical abnormalities. The results are shown in Table IV.

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